

PRELIMINARY AMENDMENT

Serial Number: 09/943,420

Filing Date: August 30, 2001

Title: SODIUM CHANNEL MODULATORS

Page 2

Dkt: 1343.008US1

copy
each R³ is independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, oxo, or heterocyclyl; and each R⁴ is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, or R^b; or R³ and R⁴ are joined to form a C₁₋₄ alkylene group, wherein the alkylene group is optionally substituted with 1 to 4 substituents independently selected from R^b;

B1
each R⁵ and R⁶ is independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl; or R⁵ and R⁶ together with the carbon atom to which they are attached form a ring having from 5 to 7 ring atoms, wherein the ring optionally contains 1 or 2 heteroatoms in the ring independently selected from oxygen, sulfur or nitrogen;

wherein for R¹-R⁶, each alkyl, alkenyl, and alkynyl is optionally substituted with R^x, or with 1, 2, 3, or 4 substituents independently selected from R^b; for R¹-R⁶, each aryl and heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c, and for R¹-R⁶, each cycloalkyl and heterocyclyl is optionally substituted with 1 to 4 substituents independently selected from R^b and R^c;

each R^a is independently -OR^d, -NO₂, halo, -S(O)_mR^d, -SR^d, -S(O)₂OR^d, -S(O)_mNR^dR^e, -NR^dR^e, -O(CR^fR^g)_nNR^dR^e, -C(O)R^d, -CO₂R^d, -CO₂(CR^fR^g)_nCONR^dR^e, -OC(O)R^d, -CN, -C(O)NR^dR^e, -NR^dC(O)R^e, -OC(O)NR^dR^e, -NR^dC(O)OR^e, -NR^dC(O)NR^dR^e, -CR^d(=N-OR^e), -CF₃, or -OCF₃;

each R^b is independently R^a, oxo or =N-OR^e;

each R^c is independently R^a, alkyl, alkenyl, or alkynyl; wherein each alkyl, alkenyl and alkynyl is optionally substituted with 1 to 4 substituents independently selected from R^b;

each R^d and R^e is independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl; wherein each alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with 1 to 4 substituents independently selected from R^b; or R^d and R^e together with the atoms to which they are attached form a heterocyclic ring having from 5 to 7 ring atoms, wherein the heterocyclic ring optionally contains 1 or 2 additional heteroatoms independently selected from oxygen, sulfur or nitrogen;

each R^f and R^g is independently hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl; wherein each alkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with 1 to 4 substituents independently selected from R^b; or R^f and R^g together with

PRELIMINARY AMENDMENT

Serial Number: 09/943,420

Filing Date: August 30, 2001

Title: SODIUM CHANNEL MODULATORS

Page 3

Dkt: 1343.008US1

contd.
B1
the carbon atom to which they are attached form a ring having from 5 to 7 ring atoms, wherein the ring optionally contains 1 or 2 heteroatoms independently selected from oxygen, sulfur or nitrogen;

each R^h is independently halo, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, (aryl)- C_{1-6} alkyl, heteroaryl, (heteroaryl)- C_{1-6} alkyl, hydroxy, amino, $-NHC_{1-6}$ alkyl, $-N(C_{1-6} \text{ alkyl})_2$, $-OC(O)C_{1-6}$ alkyl, $-C(O)C_{1-6}$ alkyl, $-C(O)OC_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-C(O)NHC_{1-6}$ alkyl, carboxy, nitro, $-CN$, or $-CF_3$;

R^k is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl; wherein each alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with 1 to 4 substituents independently selected from R^h ;

R^m is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl; wherein each alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with 1 to 4 substituents independently selected from R^h ;

each R^x is independently aryl, heteroaryl, cycloalkyl or heterocyclyl; wherein each aryl or heteroaryl is optionally substituted with 1 to 4 substituents selected from the group consisting of R^c , and wherein each cycloalkyl and heterocyclyl is optionally substituted with 1 to 4 substituents selected from R^b ;

m is 0, 1, or 2;

n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

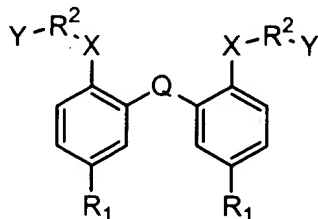
p is 1, 2, or 3;

r is 2, or 3; and

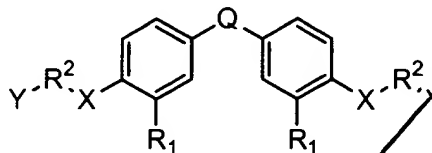
each w is independently 0, 1, 2, 3, or 4;

or a pharmaceutically-acceptable salt thereof.

41. A compound of formula XXIX or XXX:



(XXIX)



(XXX)

wherein:

Q is methylene;

each R^1 is chloro;

each R^2 is independently a covalent bond or alkylene; wherein alkylene is optionally substituted with 1 to 4 substituents independently selected from R^b ;

each X is independently oxy ($-O-$) or $-N(R^m)-$;

each Y is independently NR^nR^p or a heterocyclyl containing at least one nitrogen atom, wherein each nitrogen of the heterocyclyl is substituted with R^3 or is linked to R^2 , and wherein each heterocycle of Y is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^4 ;

each R^3 is independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, oxo, or heterocyclyl; and each R^4 is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, or R^b ; or R^3 and R^4 are joined to form a C_{1-4} alkylene group, wherein the alkylene group is optionally substituted with 1 to 4 substituents independently selected from R^b ;

wherein for R^1-R^4 , each alkyl, alkenyl, and alkynyl is optionally substituted with R^x , or with 1, 2, 3, or 4 substituents independently selected from R^b ; for R^1-R^4 , each aryl and heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c , and for R^1-R^4 , each cycloalkyl and heterocyclyl is optionally substituted with 1 to 4 substituents independently selected from R^b and R^c ;

each R^a is independently $-OR^d$, $-NO_2$, halo, $-S(O)_mR^d$, $-SR^d$, $-S(O)_2OR^d$, $-S(O)_mNR^dR^e$, $-NR^dR^e$, $-O(CR^fR^g)_nNR^dR^e$, $-C(O)R^d$, $-CO_2R^d$, $-CO_2(CR^fR^g)_nCONR^dR^e$, $-OC(O)R^d$, $-CN$, -

contd.
at
C(O)NR^dR^e, -NR^dC(O)R^e, -OC(O)NR^dR^e, -NR^dC(O)OR^e, -NR^dC(O)NR^dR^e, -CR^d(=N-OR^e), -CF₃,
or -OCF₃;

B
each R^b is independently R^a, oxo or =N-OR^e;

each R^c is independently R^a, alkyl, alkenyl, or alkynyl; wherein each alkyl, alkenyl and alkynyl is optionally substituted with 1 to 4 substituents independently selected from R^b;

each R^d and R^e is independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl; wherein each alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with 1 to 4 substituents independently selected from R^b; or R^d and R^e together with the atoms to which they are attached form a heterocyclic ring having from 5 to 7 ring atoms, wherein the heterocyclic ring optionally contains 1 or 2 additional heteroatoms independently selected from oxygen, sulfur or nitrogen;

each R^f and R^g is independently hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl; wherein each alkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with 1 to 4 substituents independently selected from R^b; or R^f and R^g together with the carbon atom to which they are attached form a ring having from 5 to 7 ring atoms, wherein the ring optionally contains 1 or 2 heteroatoms independently selected from oxygen, sulfur or nitrogen;

each R^h is independently halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, aryl, (aryl)-C₁₋₆ alkyl, heteroaryl, (heteroaryl)-C₁₋₆ alkyl, hydroxy, amino, -NHC₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, -OC(O)C₁₋₆ alkyl, -C(O)C₁₋₆ alkyl, -C(O)OC₁₋₆ alkyl, -NHC(O)C₁₋₆ alkyl, -C(O)NHC₁₋₆ alkyl, carboxy, nitro, -CN, or -CF₃;

R^m is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl; wherein each alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with 1 to 4 substituents independently selected from R^b;

each Rⁿ and R^p is independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl; wherein each alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with 1 to 4 substituents independently selected from R^b;

each R^x is independently aryl, heteroaryl, cycloalkyl or heterocyclyl; wherein each aryl or heteroaryl is optionally substituted with 1 to 4 substituents selected from the group consisting of R^c, and wherein each cycloalkyl and heterocyclyl is optionally substituted with 1 to 4 substituents

PRELIMINARY AMENDMENT

Serial Number: 09/943,420

Filing Date: August 30, 2001

Title: SODIUM CHANNEL MODULATORS

Page 6

Dkt: 1343.008US1

contd.
selected from R^b;

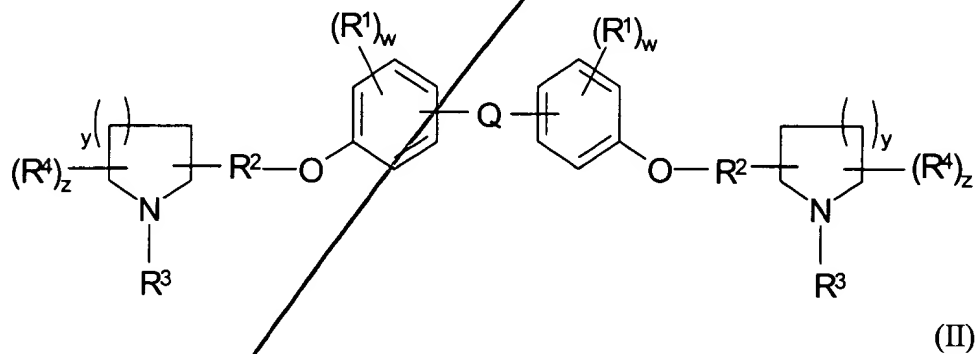
B
 m is 0, 1, or 2; and

n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

or a pharmaceutically-acceptable salt thereof;

provided that when any Y is NRⁿR^p or a nitrogen-linked heterocyclyl, then the R² attached to that Y is not a covalent bond or methylene.

42. The compound of claim 40 which is a compound of formula II:



wherein:

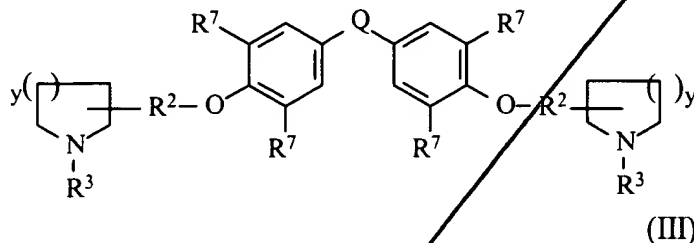
Q is -O-, -S(O)_m-, or -CR⁵R⁶-;

each y is independently 0, 1, 2, or 3; and

each z is independently 0, 1, 2, 3, or 4;

or a pharmaceutically-acceptable salt thereof.

contd. 43. The compound of claim 40 which is a compound of formula (III):



wherein

Q is -O-, -S(O)_m-, or -CR⁵R⁶-;

each R⁷ is independently hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, cycloalkyl, or R^a;

each R³ is independently hydrogen, C₁₋₁₀ alkyl, or oxo;

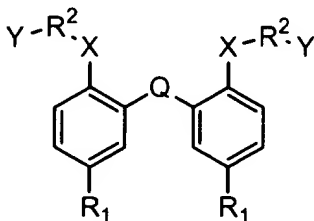
each R⁵ and R⁶ is independently hydrogen or C₁₋₁₀ alkyl; or R⁵ and R⁶ together with the carbon atom to which they are attached form a ring having from 5 to 7 ring atoms, wherein the ring optionally contains 1 or 2 heteroatoms in the ring independently selected from oxygen, sulfur and nitrogen;

wherein for R³, R⁵, R⁶, and R⁷, each alkyl, alkenyl, and alkynyl is optionally substituted with R^x, or with 1 to 4 substituents independently selected from R^b; and each cycloalkyl is optionally substituted with 1 to 4 substituents independently selected from R^b and R^c; and

each y is independently 1, 2, or 3;

or a pharmaceutically-acceptable salt thereof.

44. The compound a claim 40 which is a compound of formula XXIX:



(XXIX)

wherein:

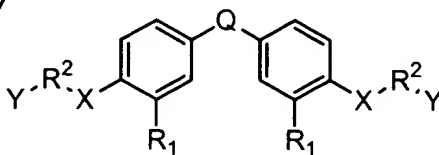
Q is methylene;

each R¹ is chloro;

each Y is independently a heterocyclyl containing at least one nitrogen atom, wherein each nitrogen of the heterocyclyl is substituted with R³; and

and R² and X have any of the values defined in claim 1; or a pharmaceutically-acceptable salt thereof.

45. The compound a claim 40 which is a compound of formula XXX:



(XXX)

wherein:

Q is methylene;

each R¹ is chloro;

each Y is independently a heterocyclyl containing at least one nitrogen atom, wherein each nitrogen of the heterocyclyl is substituted with R³; and

~~cancel~~
and R² and X have any of the values defined in claim 40; or a pharmaceutically-acceptable salt thereof.

46. The compound of claim 40 wherein each R¹ is independently C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, cycloalkyl, or R^a.

47. The compound of claim 40 wherein each R¹ is independently C₁₋₁₀ alkyl or halo.

48. The compound of claim 40 wherein each R¹ is independently methyl, ethyl, propyl, chloro, bromo, fluoro, or isopropyl.

49. The compound of claim 40 wherein each R¹ is independently methyl, or chloro.

50. The compound of claim 40 or 41 wherein each R² is independently a covalent bond or C₁₋₁₀ alkylene.

51. The compound of claim 40 or 41 wherein each R² is independently a covalent bond, methylene, 1,2-ethylene, 1,3-propylene, (2R)-2-(methyl)ethane-1,2-diyl, (2S)-2-(methyl)ethane-1,2-diyl, 1-(methyl)butane-1,4-diyl, 1-(methyl)ethane-1,2-diyl, or 2,2-(dimethyl)propane-1,3-diyl.

52. The compound of claim 40 or 41 wherein each R² is independently a covalent bond, methylene, or ethylene.

53. The compound of claim 40 wherein Q is -O-, -S(O)_m-, or -(CR⁵R⁶)_p-.

54. The compound of claim 40 wherein Q is -O-, -S(O)_m-, or -N(R^k)-

55. The compound of claim 40 wherein Q is -(CR⁵R⁶)_p-, or -O(CR⁵R⁶)_rO-

- contd.*
a1
56. The compound of claim 40 wherein Q is -O-, -S(O)_m-, -(CR⁵R⁶)_p-, or -N(R^k)-;
57. The compound of claim 40 wherein Q is methylene, 1,2-ethylene, 3,4-hexylene, dimethylmethylene, oxy, -NH-, -OCH₂CH₂O-, or a group -C(R⁵)(R⁶)- wherein R⁵ and R⁶ together with the carbon to which they are attached form a cyclohexylene ring.
58. The compound of claim 40 or 41 wherein each X is oxy.
59. The compound of claim 40 or 41 wherein each X is -NH-.
60. The compound of claim 41 wherein each Y is independently NRⁿR^p.
61. The compound of claim 41 wherein each Y is independently a heterocyclyl containing at least one nitrogen atom, wherein each nitrogen of the heterocyclyl is substituted with R³ or linked to R², and wherein each heterocycle of Y is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R⁴.
62. The compound of claim 41 wherein each Y is independently a heterocyclyl containing at least one nitrogen atom, wherein each nitrogen of the heterocyclyl is linked to R², and wherein each heterocycle of Y is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R⁴.
63. The compound of claim 40 or 41 wherein each Y is independently a heterocyclyl selected from pyrrolidinyl, piperidinyl, and morpholinyl, wherein each heterocycle of Y is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R⁴.
64. The compound of claim 41 wherein Y is independently amino, diethylamino, dimethylamino, 1-methyl-4-piperidinyl, 1-methyl-3-piperidinyl, 1-methyl-2-piperidinyl, 4-piperidinyl, 3-piperidinyl, 2-piperidinyl, 1-isopropyl-3-pyrrolidinyl, morpholino, (2R,4R)-2-

PRELIMINARY AMENDMENT

Serial Number: 09/943,420

Filing Date: August 30, 2001

Title: SODIUM CHANNEL MODULATORS

Page 11

Dkt: 1343.008US1

contd.
methoxycarbonyl-4-pyrrolidinyl, 1-methyl-3-pyrrolidinyl, 1-methyl-2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolidinyl, 1-pyrrolidinyl, (2S,4R)-2-methyl-4-pyrrolidinyl, (2R,4R)-2-carboxy-4-pyrrolidinyl, (2S,4S)-2-(N,N-dimethylamino)carbonyl-4-pyrrolidinyl, (2R,4R)-2-hydroxymethyl-4-pyrrolidinyl, or (2R,4R)-2-methoxymethyl-4-pyrrolidinyl.

B
65. The compound of claim 40 wherein each w is 0.

66. The compound of claim 40 wherein each w is 1.

67. The compound of claim 40 wherein each w is 2.

68. The compound of claim 42 or 43 wherein each y is independently 1 or 2.

69. The compound of claim 42 wherein each z is independently 0, 1, or 2.

70. The compound of claim 40 which is a compound of any one of formulae V-XXX, shown in Figures 1-3, wherein X, Y, Q, R^1 , R^2 , and w have the values given in claim 40.

71. The compound of claim 40, which is any one of compounds 1-11 shown in Table 1; or a pharmaceutically acceptable salt thereof.

72. A pharmaceutical composition comprising a compound as described in claim 40 or 41; and a pharmaceutically acceptable carrier.

73. A method of treating a disease or condition associated with sodium channel activity in a mammal, comprising administering to the mammal, a therapeutically effective amount of a pharmaceutical composition of claim 72.